

released information in June 1996 that, in March 1991, U.S. forces demolished Iraqi weapon-storage sites in the Khamisiyah region. After the demolition, the sites were determined to have contained chemical warfare agents (e.g., the nerve agents, sarin and cyclosarin), thus indicating the possibility that certain U.S. troops may have been exposed for short periods of time to low levels of nerve agents (see Appendix B: *Exposure to Chemicals During the Gulf War*).

Upon return from the Gulf War, some U.S. veterans reported an array of general symptoms of ill health including fatigue, skin rash, headache, muscle and joint pain, memory disturbance, concentration difficulties and memory loss, shortness of breath, sleep disturbances, and diarrhea. Health concerns among some veterans still persist in 1999.

Various review panels have concluded that no single cause has been established for these symptoms of ill health (DSB, 1994; NIH, 1994a,b; IOM, 1996b; PAC, 1996a,b; 1997; U.S. Senate, 1998), but several potential explanations have been proposed including: possible exposure to low levels of chemical or biological warfare agents; use of pyridostigmine bromide pills to protect against chemical warfare nerve agents; exposure to airborne sand particles and/or oil-well fire smoke; exposure to mixtures of pesticides, insect repellents, and other chemicals; anthrax and botulinum toxoid vaccines; infectious diseases; depleted uranium; and physiological and psychological stress (see Appendix B: *Exposure to Chemicals During the Gulf War* for more details).

### **3. Illnesses Among Gulf War Veterans**

#### ***The Department of Veterans' Affairs Persian Gulf Health Registry and the Department of Defense Comprehensive Clinical Evaluation Program***

Health registries for U.S. Gulf War veterans were established in 1992 by the Department of Veterans' Affairs (DVA), the Persian Gulf Health Registry (PGHR), and in 1994 by the DoD, the Comprehensive Clinical Evaluation Program (CCEP). These programs were established to gather information from veterans regarding their wartime exposures and health histories and to offer veterans the opportunity to have comprehensive physical and laboratory examinations of their health. Veterans who choose to participate are clinically examined (including laboratory analysis of blood and urine samples) and administered a questionnaire regarding medical and family history, symptoms, recent debilitating illnesses, and self-perceived wartime exposures to specific risk factors (e.g., combat and specific chemicals) (Joseph et al., 1997; PGVCB, 1995).

Participation in these health registries is voluntary. The registries provide useful information to describe the health status of participants, but general prevalence rates of illnesses among Gulf War veterans cannot be assessed because participants are self-selected and do not constitute a representative sample of all U.S. soldiers who served in the Gulf region. Furthermore, no control group is available for comparison of rates of illness.

Table 1 cites the frequencies of diagnoses and the most frequent symptoms recorded for 20,000 participants in the CCEP registry through April 1, 1996 (DoD, 1996; Joseph et al., 1997). The diagnostic categories are based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) established by the U.S. Department of Health and Human Services (DHHS, 1998).

Table 1. Frequencies of symptoms and diagnoses for 20,000 Gulf War veterans participating in the DoD Comprehensive Clinical Evaluation Program (CCEP - through April 1, 1996). Adapted from DoD, 1996 (symptoms) and Joseph et al., 1997 (diagnoses).		
<b>Self-reported Symptoms</b> (13 most frequent symptoms: 10% of participants had no complaints)	<b>Chief Complaint (%)</b>	<b>Any Complaint (%)</b>
Joint pain	11	49
Fatigue	10	47
Headache	7	39
Memory loss	4	34
Sleep disturbance	2	32
Skin rash	7	31
Difficulty concentrating	<1	27
Depression	1	23
Muscle pain	1	21
Diarrhea	2	18
Dyspnea (shortness of breath)	3	18
Abdominal/gastrointestinal pain	3	17
Hair loss	<1	12
<b>Diagnostic Category</b>	<b>Primary Diagnosis</b>	<b>Secondary Diagnosis</b>
Disease of musculoskeletal system & connective tissue	18.6	29.5
Mental disorders	18.3	17.9
Symptoms, signs, ill-defined conditions	17.8	32.6
Respiratory system diseases	6.8	10.8
Skin and subcutaneous tissue diseases	6.3	13.7
Digestive system diseases	6.2	14.1
Nervous system & sense organ diseases	5.8	12.3
Infectious and parasitic diseases	2.6	6.4
Circulatory system diseases	2.2	5.9
Endocrine, nutritional & metabolic diseases & immunity disorders	2.1	6.1
Genitourinary diseases	1.3	4.2
Injury and poisoning	0.8	2.4
Neoplasms	0.8	2.1
Blood & blood-forming organ diseases	0.6	2.6
Congenital anomalies: conditions originating in perinatal period	0.2	0.9

Table 2 lists the ten most frequent self-reported symptoms and the distribution of diagnoses for 52,835 participants in the DVA PGHR, as of August 1997, showing similar frequencies of symptoms and diagnoses as those in the DoD CCEP (DVA, 1998a).

A more recent combined analysis of data in both the DoD and DVA registries through December 1997 (DVA, 1997 as cited in U.S. Senate, 1998) indicated that the frequencies of diagnoses were similar to the CCEP analysis by Joseph et al. (1997). Both registries indicate that there is concern among veterans regarding their health: 85,000 U.S. Gulf War veterans participated in the two clinical programs through 1997 (DVA, 1997 as cited in U.S. Senate, 1998).

Table 2. Frequencies of self-reported symptoms and diagnoses in 52,835 participants in the DVA Persian Gulf Health Registry (PGHR). Data as of August, 1997. Source: DVA, 1998a.		
Symptoms	Number	Percent
Fatigue	10,847	20.5
Skin rash	9,719	18.4
Headache	9,525	18.0
Muscle, joint pain	8,871	16.8
Loss of memory and other general symptoms	7,406	14.0
Shortness of breath	4,190	7.9
Sleep disturbances	3,111	5.9
Diarrhea and other gastrointestinal symptoms	2,416	4.6
Other symptoms involving skin and integumentary tissue	1,916	3.6
Chest pain	1,847	3.5
No complaint	6,496	12.3
Diagnostic Category	Number	Percent
No medical diagnosis	13,998	26.5
Musculoskeletal and connective tissue	13,299	25.2
Mental disorders	7,995	15.1
Respiratory system	7,540	14.3
Skin & subcutaneous tissue	7,144	13.5
Digestive system	6,028	11.4
Nervous system	4,398	8.3
Circulatory system	3,747	7.1
Infectious diseases	3,715	7.0
Injury and poisoning	2,485	4.7
Genitourinary system	1,774	3.4
Neoplasm	232	0.4

In 1993, the British Ministry of Defence established a clinical assessment program, the Medical Assessment Programme, for British Gulf War veterans that is similar to the DVA PGVHR and the DoD CCEP (Coker, 1996). Among the approximately 51,000 British troops who were deployed to the Gulf region, 1,026 registered in this program by June 1996, and 608 completed the program. Coker (1996) reported on an analysis of information for 284 of the veterans who completed the program. Although from a much smaller study population, the frequencies of

symptoms and diagnoses among the examined British Gulf War veterans (see Table 3) show some similarities to the results in Tables 1 and 2.

Table 3. Frequencies of Symptoms and Diagnoses for 284 participants in the British Ministry of Defence Medical Assessment Programme. Adapted from Coker, 1996.	
Symptom	Subjects reporting symptom (%)
Tiredness	55%
Muscle & joint pain	35%
Irritability	29%
Sleep disturbance	24%
Short-term memory loss	22%
Breathlessness	21%
Skin problems	16%
Tingling in limbs	11%
Principal Diagnostic Category (using ICD-9)	Frequency
Psychological conditions	35%
Signs, symptoms, and ill-defined conditions & chronic fatigue syndrome	15%
Respiratory system	9%
Skin and subcutaneous tissue	8%
Digestive system	7%
Nervous system	6%
Musculoskeletal system & connective tissue	6%
Circulatory system	3%
Genitourinary system	2%
Infectious diseases	1%
Endocrine	1%
Neoplasms	1%

The frequencies and types of symptoms and diagnoses of illnesses in participants in these clinical programs show that:

- C common health problems involve a wide variety of organ systems including the musculoskeletal, gastrointestinal, respiratory, and nervous systems;
- C a significant proportion of participants (20-30%) reported common symptoms (e.g., fatigue, headache, nervousness, heartburn, insomnia) that were without a clear physiologic or psychologic basis. Clinicians were not able to assign a standard diagnosis to these patients other than *symptoms, signs and ill-defined conditions*; and
- C three diagnostic categories (psychological conditions, musculoskeletal diseases, and symptoms, signs and ill-defined conditions) represented more than 50% of the primary diagnoses.

The most frequent symptoms reported as a chief complaint by the 3,558 DoD CCEP participants who were assigned to the diagnostic category, *symptoms, signs, ill-defined conditions*, were: fatigue (20%), headache (9.2%), memory problems (6.3%), sleep disturbances (4.7%), skin rash (4.4%), joint pain (4.2%), and shortness of breath (1.8%) (Joseph et al., 1997). Twenty-six percent (914/3558) of these participants reported multiple symptoms without designating a chief complaint.

Hyams et al. (1996) noted that symptom patterns for Gulf War veterans are consistent with the experiences of U.S. veterans of previous wars. Reviewing English-language articles and books of war-related illnesses associated with the Civil War, World Wars I and II, the Korean Conflict, and the Vietnam War, Hyams recognized two general categories of war-related illnesses that were diagnosed after each of these wars: 1) psychological illnesses<sup>2</sup>; and 2) physiological illnesses<sup>3</sup>. The physiological illnesses were primarily defined by self-reported, chronic (i.e., long-lasting) symptoms including fatigue, shortness of breath, headache, sleep disturbances, impaired concentration, and forgetfulness. Hyams noted that these symptoms are non-specific and are frequently found in all adult populations, as well as among persons with illnesses associated with psychological stress, and that, in each of these wars, the onset of these illnesses was preceded by a high frequency of diarrhea. Hyams concluded that “poorly understood war syndromes” have recurred since the U.S. Civil War, that no single disease or underlying cause that is unrelated to psychological stress is apparent from his review, and that the relationships between chronic, non-specific symptoms and physiological and psychological illness need to be better understood.

Because of the limitations of the information from the health registry programs<sup>4</sup>, the DVA is conducting a three-phase National Health Survey of Gulf War veterans to obtain estimates of nationally representative prevalences of symptoms and other medical conditions among all U.S. Gulf War veterans, (DVA research project # 2; RWG, 1998, 1999). Phase 1 involved mailing a questionnaire to 30,000 randomly selected U.S. veterans (15,000 Gulf War veterans and 15,000 veterans who served during the period of the Gulf War, but were not deployed to the Gulf region). Phase 2 interviewed, by telephone, a sample of 8,000 non-respondents, and validated (through records review) self-reported data for randomly selected respondents (2,000 deployed and 2,000 non-deployed). Phase 3 involves comprehensive clinical examination of the 4,000 respondents (and their families) selected in Phase 2. Analysis of collected data is not available to date.

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<sup>2</sup> Given various names through the years from *nostalgia* in the Civil War, through *shell shock* in WWI, and *battle fatigue* in WWII and Korea, to *post-traumatic stress disorder* after the Vietnam and Gulf Wars.

<sup>3</sup> *Da Costa syndrome* (irritable heart) after the Civil War, *Effort syndrome* during and after WWI and II, *Agent Orange exposure* after Vietnam, and *Gulf War syndrome*.

<sup>4</sup> For example, participants are not a random sample of all Gulf War veterans and there is no control group to compare prevalences.

## ***Conclusions and Research Recommendations from Review Panels***

Four panels of experts have evaluated available data from the DoD and DVA health registries and other sources of information regarding illnesses among Gulf War veterans: the *Defense Science Board Task Force on Persian Gulf War Health Effects* (DSB, 1994); the *National Institutes of Health Technology Assessment Workshop Panel* (NIH, 1994a,b); the *Institute of Medicine Committee to Review the Health Consequences of Service During the Persian Gulf War* (IOM, 1996b); and the *Presidential Advisory Committee on Gulf War Veterans' Illnesses* (PAC, 1996a,b; 1997). Appendix A of this document provides an historical account of the establishment of these and other panels reviewing various aspects of illnesses among Gulf War veterans and also summarizes panel recommendations. Each of the panels concluded that there was no evidence consistent with the existence of a unique disease among Gulf War veterans (DSB, 1994; NIH, 1994a,b; IOM, 1996b; PAC, 1996a,b, 1997).

The panels considered a number of suggested causes of illnesses among Gulf War veterans including combat- and deployment-related stress, chemical and biological warfare agents, vaccines, pesticides, pyridostigmine bromide, infectious diseases, depleted uranium, smoke from oil-well fires, petroleum products, and exposures to mixtures of chemicals specific to the Gulf War experience (see Appendix B: *Exposure to Chemicals During the Gulf War* for further discussion of potential Gulf War health risk factors). Given the broad range of illnesses noted among Gulf War veterans and the incomplete exposure data that were available, each of the panels concluded that no single cause of the multiple illnesses could be established (DSB, 1994; NIH, 1994a,b; IOM, 1996b; PAC, 1996a,b, 1997). The Presidential Advisory Committee on Gulf War Veterans' Illnesses made three further conclusions that: 1) it was unlikely that the reported illnesses were caused by exposure to any of the previously mentioned physical risk factors; 2) stress was likely to be an important contributing risk factor; and 3) research should be pursued in areas of uncertainty, such as the long-term effects of low-level exposure to chemical warfare agents and the synergistic effects of exposure to pyridostigmine bromide and other risk factors (PAC, 1996a,b, 1997; Lashof and Cassells, 1998).

The Presidential Advisory Committee further recommended that, "To ensure credibility and thoroughness, further investigation of possible chemical or biological warfare agent exposures during the Gulf War should be conducted by a group independent of DoD." (PAC, 1996b, 1997). In response to this recommendation, President Clinton created the Special Oversight Board for Department of Defense Investigations of Gulf War Chemical and Biological Incidents "to provide advice and recommendations based on review of DoD investigations into possible detections of, and exposures to, chemical or biological weapons agents and environmental and other factors that may have contributed to Gulf War Illnesses" (PSOB, 1998). This group held its first public hearing in November, 1998.

In response to another recommendation from the Presidential Advisory Committee (PAC, 1997), the DVA contracted the Institute of Medicine of the National Academy of Sciences to conduct a periodic review of scientific evidence regarding associations between illnesses and Gulf War

service. To carry out this review, the Institute of Medicine Committee on Health Effects Associated with Exposures During the Gulf War was formed in 1998 and held its first meeting in January 1999 (IOM, 1998a).

Initial research recommendations from the review panels included:

- C epidemiological research to compare prevalence rates of illnesses in Gulf War veterans with appropriate control populations;
- C research to examine groups of symptomatic Gulf War veterans more closely with neuropsychological and psychological tests; and
- C research on specific risk factors such as stress, pesticides, depleted uranium, and Leishmaniasis (DSB, 1994; NIH, 1994a,b; IOM, 1996b; PAC, 1996a).

More recent research recommendations include:

- C research into the long-term effects of low-level exposure to chemical warfare agents, alone and in combination with exposure to other Gulf War health risk factors including stress, pesticides and pyridostigmine bromide;
- C epidemiological research on groups of U.S. troops known to be in the vicinity of Khamisiyah when low-level exposure to nerve agents may have occurred;
- C research emphasis should include investigations of the causes, methods of prevention, and methods of treatment of musculoskeletal conditions and stress-related disorders (PAC, 1996b, 1997).

The Institute of Medicine established the Committee on Measuring Health Status of Persian Gulf Veterans in 1998 to identify important research questions regarding Gulf War illnesses and develop research designs and methods to address the questions (IOM, 1998b). The committee held a workshop in May 1998 (IOM, 1998c), but the committee's findings and recommendations are not yet available.

Overviews of research results and ongoing research on illnesses among Gulf War veterans are presented in sections 5 and 6 and Appendices C and D of this document.

#### **4. Overview: U.S. Government-Supported Research on Gulf War Illnesses**

In response to Public Law 102-585, President Clinton, in August, 1993, named the Secretary of Veterans Affairs to coordinate executive branch-funded research on the health consequences of the Gulf War. The Persian Gulf Veterans Coordinating Board (PGVCB) was formed in January, 1994 to coordinate interagency efforts in research, clinical care, disability compensation, resource allocation, and information dissemination. The Secretaries of the DoD, the DVA, and the DHHS chair the PGVCB. The RWG was established to assess the state and direction of research, identifying gaps in factual knowledge and conceptual understanding, identify testable hypotheses, recommend research directions for participating agencies, review research concepts as they are developed, and collect and disseminate scientifically peer-reviewed information (RWG, 1998).